REMARKS

The amendments of Claim 1 are intended merely as clarifying amendments. They do not, and are not intended to, change the scope of Claim 1. Support for the amendment of Claim 1 to specify that the peptide does not have metal ion bound to it when it is administered to animals may be found throughout the application, including on page 7, lines 2-5, and page 13, lines 19-27, and in Examples 8-9, of the present application.

New Claims 375-381 have been added. Support for these new claims is found at, *e.g.*, page 33, line 1, and page 33, line 9 through page 34, line 6, of the present application.

After the above amendments, Claims 1-26, 28-31 and 375-381 are pending.

A. Restriction Requirement

The Examiner continues to maintain the restriction requirement with respect to subgenera G1 and G2. Applicants also continue to traverse this restriction requirement for the reasons of record. However, Applicants understand from the Examiner's remarks that this requirement will be withdrawn if the currently pending claims, which are considered to be generic claims encompassing both subgenera G1 and G2, are found allowable.

B. Objections to the Specification

On page 6, line 7, of the specification, the Examiner has asked that the web address be deleted because such addresses are transient. Applicants do not believe it is necessary to do so. First, this address is still present on the web as of today. If it should be taken off the web at some time in the future, an alternate citation is provided (the abstracts of the Speciation 98 meeting).

The Examiner has also pointed out an error in Figures 1A-1D. Applicants are submitting herewith amended drawings of Figures 1A-1D to correct this obvious error.

C. Section 112 Rejections

The Examiner has rejected Claim 27 on the basis that it is not enabled and on the basis that it is indefinite. Claim 27 has been canceled, without prejudice or disclaimer of its subject matter, by the above amendments, so these rejections are moot.

D. Section 103 Rejections

1. Rejection of Claims 1 and 8-11

The Examiner has rejected Claims 1 and 8-11 as being unpatentable over Dunphy *(Am. J. Physiol.*, **276**, H1591-1598 (1999)) in view of Carter (U.S. Patent No. 5,780,594). It is the Examiner's position that:

> Dunphy discloses that albumin reduces the damage done by reactive oxygen species. Dunphy does not disclose that the third amino acid from the N-terminus is histidine. Carter discloses . . . the sequence of human albumin. As is evident, the N-terminal peptide is D-A-H-K, which coincide with SEQ ID NO:1 of the instant application.
>
> Thus, it would have been obvious that a peptide which conforms with the formula P1-P2 is effective to reduce the damage done by reactive oxygen species.

Applicants respectfully traverse this rejection.

All of the teachings of the prior art must be considered in an obviousness rejection, including those contrary to the Examiner's position.[1] When those teachings contrary to the Examiner's position are considered in the present case, it is readily evident that the Examiner has not even established a *prima facie* case of obviousness.

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[1] See *In re Dow Chem. Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988); *In re Evanega*, 829 F.2d 1110, 4 USPQ2d 1249 (Fed. Cir. 1987); *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987); *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 USPQ2d 1593 (Fed. Cir. 1987); *Akzo N.V. v. United States I.T.C.*, 808 F.2d 1471, 1 USPQ2d 1241 (Fed. Cir. 1986); *Ashland Oil, Inc. v. Delta Resins & Refracs., Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985); *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 227 USPQ 337 (Fed. Cir. 1985); *EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 225 USPQ 20 (Fed. Cir. 1985); *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984).

First, as described in the present application, there were conflicting reports in the prior art as to whether albumin did or did not reduce the damage done by reactive oxygen species (ROS). See page 3, line 11, through page 5, line 7, of the present application. Albumin has even been reported to cause the production of ROS. See page 5, lines 1-7, of the present application. Dunphy itself contains conflicting teachings about the effectiveness of albumin. See page 4, lines 11-28, of the present application. Thus, it was quite unsettled in the prior art as to whether albumin could reduce the damage done by ROS.

Second, for the reasons described in detail below, Carter actually teaches away from the presently claimed invention. In particular, the present claims are directed to the use of a peptide P_1-P_2 to reduce the damage done by ROS. Peptide P_1-P_2 has at most 104 amino acids (see Claim 1 and the definition of n). Human albumin contains 585 amino acids, so P_1-P_2 does not include intact albumin. P_1-P_2 can correspond to fragments of human albumin which include the N-terminus of human albumin. See page 14, lines 19-22, of the present application.

Those references reporting that albumin could function as an antioxidant attributed this ability to several of albumin's many physiological functions. See page 3, lines 14-17, of the present application. Thus, those skilled in the art would not have known which portion(s) of albumin were responsible for the alleged antioxidant activity of albumin and certainly would not have concluded that the N-terminus of albumin was necessary for this activity.

The Carter patent cited by the Examiner reports that the biological activities of albumin reside in subdomains of the molecule that do not include the N-terminus of albumin. See, *e.g.*, column 2, line 50 through column 3, line 6; see also Figure 2 of Carter. Thus, Carter actually teaches away from the presently claimed invention. Moreover, contrary to the Examiner's contention, even assuming that albumin could reduce the damage done by ROS, which the prior art taught was quite uncertain, those skilled in the art would not have been motivated by Carter to use an N-terminal portion of albumin to reduce the damage done by ROS.

For all of the foregoing reasons, the Examiner has not even established a *prima facie* case of obviousness. It was quite unsettled in the prior art whether albumin could reduce the damage

done by ROS, it was not known which portion(s) of albumin might be responsible for any antioxidant activity that albumin might have, and Carter taught away from the N-terminus of albumin as being responsible for the any of the biological activities of albumin. Accordingly, this rejection should be withdrawn.

2. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over Gutteridge *(Biochim Biophys Acta*, **759**, 38 (1983)) in view of Carter (U.S. Patent No. 5,780,594). It is the Examiner's position that:

> Gutteridge discloses that albumin reduces the damage done by reactive oxygen species. Gutteridge does not disclose that the third amino acid from the N-terminus is histidine. Carter discloses . . . the sequence of human albumin. As is evident, the N-terminal peptide is D-A-H-K, which coincide with SEQ ID NO:1 of the instant application.
>
> Thus, it would have been obvious that a peptide which conforms with the formula P1-P2 is effective to reduce the damage done by reactive oxygen species.

Applicants respectfully traverse this rejection.

All of the teachings of the prior art must be considered in an obviousness rejection, including those contrary to the Examiner's position.[2] When those teachings contrary to the Examiner's

position are considered in the present case, it is readily evident that the Examiner has not even established a *prima facie* case of obviousness.

First, as described in the present application, there were conflicting reports in the prior art as to whether albumin did or did not reduce the damage done by ROS. See page 3, line 11, through page 5, line 7, of the present application. Albumin has even been reported to cause the production of ROS. See page 5, lines 1-7, of the present application. Thus, it was quite unsettled in the prior art as to whether albumin could reduce the damage done by ROS.

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[2] See those cases cited in footnote 1 above.

Second, for the reasons described in detail below, Carter actually teaches away from the presently claimed invention. In particular, the present claims are directed to the use of a peptide P_1-P_2 to reduce the damage done by ROS. Peptide P_1-P_2 has at most 104 amino acids (see Claim 1 and the definition of n). Human albumin contains 585 amino acids, so P_1-P_2 does not include intact albumin. P_1-P_2 can correspond to fragments of human albumin which include the N-terminus of human albumin. See page 14, lines 19-22, of the present application.

Those references reporting that albumin could function as an antioxidant attributed this ability to several of albumin's many physiological functions. See page 3, lines 14-17, of the present application. Thus, those skilled in the art would not have known which portion(s) of albumin were responsible for the alleged antioxidant activity of albumin and certainly would not have concluded that the N-terminus of albumin was necessary for this activity.

The Carter patent cited by the Examiner reports that the biological activities of albumin reside in subdomains of the molecule that do not include the N-terminus of albumin. See, *e.g.*, column 2, line 50 through column 3, line 6; see also Figure 2 of Carter. Thus, Carter actually teaches away from the presently claimed invention. Moreover, contrary to the Examiner's contention, even assuming that albumin could reduce the damage done by ROS, which the prior art taught was quite uncertain, those skilled in the art would not have been motivated by Carter to use an N-terminal portion of albumin to reduce the damage done by ROS.

For all of the foregoing reasons, the Examiner has not even established a *prima facie* case of obviousness. It was quite unsettled in the prior art whether albumin could reduce the damage done by ROS, it was not known which portion(s) of albumin might be responsible for any antioxidant activity that albumin might have, and Carter taught away from the N-terminus of albumin as being responsible for the any of the biological activities of albumin. Accordingly, this rejection should be withdrawn.

3. Rejection of Claim 1

The Examiner has rejected Claim 1 as being unpatentable over Halliwell *(Arch. Biochem. Biophys.*, **246**, 501 (1986)). It is the Examiner's position that:

> Halliwell discloses, or at least implies, that SOD and catalase reduce the damage done by 'ROS'. Halliwell does not disclose that SOD and catalase both contain histidines. . . . [T]he claim encompasses the possibility of the histidine being present at virtually any position in the peptide . . .. This is because of the term 'having'. . . . . Accordingly, claim 1 encompasses the use of any histidine-containing peptide.

Applicants respectfully traverse this rejection.

It is the Examiner's contention that Claim 1 encompasses the use of any histidine-containing peptide. Even if this were a correct interpretation of Claim 1, which Applicants strongly contend it is not, the rejection is fatally flawed since the Examiner never demonstrates that SOD or catalase contains a histidine. Indeed, the Examiner expressly states that Halliwell, the only cited prior art reference, does not disclose that SOD or catalase contains histidine. Accordingly, the Examiner has not even established a *prima facie* case of obviousness, and Applicants respectfully request that this rejection be withdrawn.

Even though the foregoing remarks are sufficient to overcome the rejection, Applicants want to point out that the Examiner's interpretation of Claim 1 is incorrect. Claim 1 is directed to the use of a peptide P_1-P_2 to reduce the damage done by ROS. In Claim 1, it is expressly stated that the N-terminal amino acid of this peptide P_1-P_2 is Xaa_1. It necessarily follows, therefore, that histidine must be the third amino acid from N-terminus of the peptide. The use of the term "having" (which has been eliminated by the above amendments to Claim 1) did not change this interpretation.

4. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over Ueda *(J. Inorg. Biochem.*, **55**, 123 (1994)). It is the Examiner's position that:

> Ueda dicloses that the tripeptide Gly-Gly-His mimics the effect of SOD in dismuting superoxide. Also disclosed . . . is that H_2O_2 is converted to water and O_2 by catalase.

> Thus, it would have been obvious to one of ordinary skill that Gly-Gly-His is effective to 'scavenge' at least one reactive oxygen specie. . . . In addition, it would have been obvious that by contacting a combination of Cu(II)-Gly-Gly-His and catalase with superoxide, the formation of ROS will be decreased, and hence the damage done be [sic, by] ROS will be reduced. [The instant claims do not preclude the simultaneous administration of multiple agents].

Applicants respectfully traverse this rejection.

Ueda presents results showing that certain copper-peptide complexes can scavenge superoxide (see Table 3 of Ueda). These results suggested to the authors that the complexes had SOD-like activity. One of these copper-peptide complexes was Cu(II)-Gly-Gly-His.

However, Ueda also teaches that the copper-peptide complexes increased the production of more active hydroxyl radical from hydrogen peroxide (see Tables 1 and 2 of Ueda). Thus, it is unclear from Ueda whether the copper-peptide complexes taught by the reference would overall reduce the production of ROS and the damage they cause. See the paragraph bridging pages 123-124 of Ueda.

The peptides of the present invention are not bound to copper or any other metal when they are administered to animals. As a result, the peptides can bind metal ions present in the animals that cause the production or accumulation of ROS. See, *e.g.*, page 1, lines 7-13, and page 13, line 19 through page 14, line 2, of the present application. It is in this manner that the peptides of the invention reduce ROS and the damage that they cause.

There is no teaching or suggestion in Ueda that the peptides taught by that reference should be used alone (*i.e.*, not complexed to copper). In particular, there is no teaching or suggestion in Ueda that the peptides would have SOD or any other activity when used alone. Accordingly, Ueda would not have taught or suggested the present invention.

The Examiner is correct that the present claims do not preclude the possibility of administering other agents together with the peptides of the invention. However, the claims cover the administration of a peptide, not a copper-peptide complex, in combination with other agents.

For the foregoing reasons, Ueda would not have made the claimed invention obvious, and this rejection should be withdrawn.

5. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over Das *(Meth. Enzymol.*, **233**, 601 (1994)) in view of Satoh (U.S. Patent No. 5,051,406) further in view of Carter (U.S. Patent No. 5,780,594). It is the Examiner's position that:

> Das discloses that antioxidants such as tocopherol can be used to reduce the damage done by 'ROS'. . . . Satoh discloses that by combining drugs with albumin, improved results are obtained. Tocopherol is also specifically mentioned . . . . . Carter discloses that in albumin, histidine is the third amino acid from the N-terminus.
>
> Thus, it would have been obvious that by combining an antioxidant such as tocopherol with albumin, the practioner [sic, practitioner] would be meeting both of the following objectives:
>
> (a) administration of a 'first' agent which inhibits damage caused by ROS, and
>
> (b) administration of a 'second' agent which contains a histidine at the requisite position.
>
> The claims do not preclude administering multiple agents.

Applicants respectfully traverse this rejection.

The present claims are directed to the use of a peptide P_1-P_2 to reduce the damage done by ROS. The peptide contains a histidine as the third amino acid from the N-terminus. The combined teachings of the references do not teach or suggest that a peptide having a histidine as the third amino acid can be used to reduce the damage done by ROS.

The Examiner is correct that the claims do not preclude administering multiple agents, meaning, of course, that another agent could be administered in addition to the peptide P_1-P_2. However, contrary to the contentions of the Examiner, the claims do not cover the use of the multiple agents described by the Examiner to substitute for the peptide P_1-P_2.

For the foregoing reasons, the combined teachings of the prior art would not have made the presently claimed invention obvious, and this rejection should be withdrawn.

6. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over Kimoto et al. *(Cancer Research*, **43**, 824 (1983))[3] in view of Malins (*Proc. Nat'l Acad. Sci.*, **93**, 2557 (1996)). It is the Examiner's position that:

> Kimoto discloses a process which 'comprises' administration of the peptide Gly-Gly-His, with the result that growth of tumor cells is inhibited. Kimoto does not disclose that tumor cell growth is caused by reactive oxygen species. Malins . . . disclose[s] that tumor cell growth is caused at least in part by reactive oxygen species.
>
> One of ordinary skill in the art would have expected that by administering the peptide Gly-Gly-His to a tumor-bearing mammal, reduction of tumor volumes can be achieved. Claim 1 requires that the damage caused by ROS be mitigated in some way. In this case, the "damage' is proliferation of tumor cells. By inhibiting the proliferation of tumor cells, the "damage" caused by ROS will be mitigated.

Applicants respectfully traverse this rejection.

The peptides of the present invention are not bound to copper or any other metal when they are administered to animals. The peptides bind metal ions present in the animals that cause the production or accumulation of ROS. See, *e.g.*, page 1, lines 7-13, and page 13, line 19 through page 14, line 2, of the present application. It is in this manner that the peptides of the invention reduce ROS and the damage that they cause.

Kimoto reports that a Cu(II)-Gly-Gly-His complex has anti-tumor activity when used in combination with a large amount of ascorbate (see the Abstract, the paragraph bridging columns 1 and 2 on page 827, and the final two paragraphs on page 827 of Kimoto). Contrary to the Examiner's contention, Kimoto does not teach or suggest that the peptide alone (*i.e.*, not complexed to copper) has such anti-tumor activity. Indeed, Kimoto teaches that it is the copper in the Cu(II)-Gly-Gly-His complex that is responsible for the killing of tumor cells (see the paragraph bridging columns 1 and 2, page 826, and third paragraph of Discussion, page 827, of Kimoto) and that the killing of the tumor cells is caused by ROS (see first full paragraph, column

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[3] Applicants are submitting herewith the full Kimoto et al. article, and all references herein are to the full article, rather than the abstract cited by the Examiner.

1, page 827 of Kimoto and the entire Kimoto article).[4] Thus, Kimoto strongly teaches away from the present invention.

Malins adds nothing to the teachings of Kimoto. In fact, to the extent that Malins teaches "that tumor cell growth is caused at least in part by reactive oxygen species," as contended by the Examiner, its teachings conflict with those of Kimoto.

Accordingly, the combined teachings of Kimoto and Malins would not have taught or suggested the presently claimed invention, and Applicants request that this rejection be withdrawn.

7. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over Kimoto et al. *(Cancer Research*, **43**, 824 (1983)) in view of Knight (*Ann. Clin. Lab. Sci.*, **25**, 111 (1995)). It is the Examiner's position that:

> Kimoto discloses a process which 'comprises' administration of the peptide Gly-Gly-His, with the result that growth of tumor cells is inhibited. Kimoto does not disclose that tumor cell growth is caused by reactive oxygen species. . . . Knight . . . disclose[s] that tumor cell growth is caused at least in part by reactive oxygen species.
>
> One of ordinary skill in the art would have expected that by administering the peptide Gly-Gly-His to a tumor-bearing mammal, reduction of tumor volumes can be achieved. Claim 1 requires that the damage caused by ROS be mitigated in some way. In this case, the "damage' is proliferation of tumor cells. By inhibiting the proliferation of tumor cells, the "damage" caused by ROS will be mitigated.

Applicants respectfully traverse this rejection.

The peptides of the present invention are not bound to copper or any other metal when they are administered to animals. As a result, the peptides can bind metal ions present in the animals that cause the production or accumulation of ROS. See, *e.g.*, page 1, lines 7-13, and page 13, line 19 through page 14, line 2, of the present application. It is in this manner that the peptides of the invention reduce ROS and the damage that they cause.

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[4] Kimoto further teaches that the Cu(II)-Gly-Gly His complex is ineffective in the absence of the ascorbate.

Kimoto reports that a Cu(II)-Gly-Gly-His complex has anti-tumor activity when used in combination with a large amount of ascorbate (see the Abstract, the paragraph bridging columns 1 and 2 on page 827, and the final two paragraphs on page 827 of Kimoto). Contrary to the Examiner's contention, Kimoto does not teach or suggest that the peptide alone (*i.e.*, not complexed to copper) has such anti-tumor activity. Indeed, Kimoto teaches that it is the copper in the Cu(II)-Gly-Gly-His complex that is responsible for the killing of tumor cells (see the paragraph bridging columns 1 and 2, page 826, and third paragraph of Discussion, page 827, of Kimoto) and that the killing of the tumor cells is caused by ROS (see first full paragraph, column 1, page 827 of Kimoto and the entire Kimoto article).[5] Thus, Kimoto strongly teaches away from the present invention.

Knight adds nothing to the teachings of Kimoto. In fact, to the extent that Knight teaches "that tumor cell growth is caused at least in part by reactive oxygen species," as contended by the Examiner, its teachings conflicts with those of Kimoto.

Accordingly, the combined teachings of Kimoto and Knight would not have taught or suggested the presently claimed invention, and Applicants request that this rejection be withdrawn.

8. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over U.S. Patent No. 4,461,724 ("Konishi"). It is the Examiner's position that:

> Konishi discloses the use of peptides for treating ulcers. The peptides contain a histidine residue which is located 3 amino acids from the N-terminus, as required of the instant claims. Konishi does not disclose that the symptoms of ulcers are mediated by "ROS". . . . As it happens, at least some of the "damage" observed in patients stricken with ulcers is caused by ROS. . . . [I]f the Konishi compounds are indeed effective to reduce the tissue damage (or other damage) caused by ulcers, then the Konishi

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[5] Kimoto further teaches that the Cu(II)-Gly-Gly His complex is ineffective in the absence of the ascorbate.

> compounds must also be effective to mitigate the damage caused by ROS. . . . Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Konishi does teach the use of certain peptides having a histidine as the third amino acid from the N-terminus for the treatment of ulcers. However, Konishi does not teach or suggest that these peptides reduce the damage done by ROS. Indeed, as acknowledged by the Examiner, Konishi does not teach or suggest anything about ROS.

The Examiner states that: "As it happens, at least some of the "damage" observed in patients stricken with ulcers is caused by ROS." However, the Examiner has provided no evidence to support this statement, which he must do. See, *e.g.*, MPEP § 2142 (the examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness).

In particular, the Examiner has provided no evidence based on the prior art to support this statement, and it is submitted that the Examiner has improperly reconstructed the claimed invention through hindsight using Applicants' disclosure as a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner has not met in this case.

For the foregoing reasons, the Examiner has not even established a *prima facie* case of obviousness, and this rejection should be withdrawn.

9. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over Pickart (U.S. Patent No. 5,118,665). It is the Examiner's position that:

> Pickart discloses . . . that the peptide Gly-Lys-His exhibits SOD activity when complexed to manganese, and further, that the peptide is an antioxidant and can be used to treat inflammatory disorders. . . . Thus, it would have been obvious to one of ordinary skill that by administering the peptide Gly-Lys-His (together with manganese) to a mammal, damage caused by ROS can be mitigated.

Applicants respectfully traverse this rejection.

Pickart teaches that certain metal-peptide and metal-peptide-chelating agent complexes have anti-inflammatory activity. See, *e.g.*, column 2, lines 38-40, and column 6, lines 10-13, of Pickart. One of these complexes is Gly Lys His complexed to manganese, as noted by the Examiner.

There is no teaching or suggestion in Pickart to use the peptides taught by that patent alone (*i.e.*, not complexed to a metal or to a metal and a chelating agent). Indeed, Pickart expressly teaches away from doing so. See column 7, lines 49-50, of Pickart, where it is stated that unbound peptides (*i.e.*, peptides not bound to a metal or to a metal and a chelating agent) do "not serve to restore or enhance the anti-oxidative or anti-inflammatory process." Thus, Pickart teaches that the use of the peptides alone would be ineffective and is to be avoided.

The peptides of the present invention are not bound to a metal or any other compound when they are administered to animals. As a result, the peptides can bind metal ions present in the animals that cause the production or accumulation of ROS. See, *e.g.*, page 1, lines 7-13, and page 13, line 19 through page 14, line 2, of the present application. It is in this manner that the peptides of the invention reduce ROS and the damage that they cause.

Clearly, the teachings of Pickart would not have made the presently claimed invention obvious. Indeed, Pickart expressly teaches away from the present invention.

For the foregoing reasons, this rejection should be withdrawn.

10. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over Pickart (U.S. Patent No. 5,118,665) in view of Knight (*Ann. Clin. Lab. Sci.*, **25**, 111 (1995)). It is the Examiner's position that:

> Pickart discloses . . . that the peptide Gly-Lys-His exhibits SOD activity when complexed to manganese, and further, that the peptide is an antioxidant and can be used to treat inflammatory disorders. Knight discloses that the damage which accompanies inflammation is caused at least in part by "ROS". . . . Thus, it would have been obvious to one of ordinary skill that by administering the peptide Gly-Lys-His (together with manganese) to a mammal, damage caused by ROS can be mitigated.

Applicants respectfully traverse this rejection for the reasons given above in response to the rejection based on Pickart alone. Knight adds nothing to the teachings of Pickart. In particular, Knight does not contain any teachings which overcome, or any way diminish, the strong teaching away from the present invention by Pickart. Accordingly, the Examiner is asked to withdraw this rejection.

11. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over Pickart (U.S. Patent No. 5,118,665) in view of Roth (*Acta Chirugica Hungarica*, **36**, 302 (1997)). It is the Examiner's position that:

> Pickart discloses . . . that the peptide Gly-Lys-His exhibits SOD activity when complexed to manganese, and further, that the peptide is an antioxidant and can be used to treat inflammatory disorders. . . . Roth . . . discloses that the damage which accompanies inflammation is caused at least in part by "ROS". Thus, it would have been obvious to one of ordinary skill that by administering the peptide Gly-Lys-His (together with manganese) to a mammal, damage caused by ROS can be mitigated.

Applicants respectfully traverse this rejection for the reasons given above in response to the rejection based on Pickart alone. Roth adds nothing to the teachings of Pickart. In particular, Roth does not contain any teachings which overcome, or any way diminish, the strong teaching away from the present invention by Pickart. Accordingly, the Examiner is asked to withdraw this rejection.

12. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over U.S. Patent No. 5,591,711 ("Koyama"). It is the Examiner's position that:

> Koyama discloses the use of Gly-Lys-His for wound healing. Koyama does not disclose that, once tissue is wounded, further damage to that tissue is caused at least in part by "ROS". . . . As it happens, at least some of the "damage" inflicted upon wounded tissue is caused by ROS. If the Koyama peptides are indeed effective to promote wound healing, then at least some of the "damage" caused by ROS will be mitigated. . . . Thus, the claims are rendered obvious.

Applicants respectfully traverse this rejection.

Koyama teaches the use of the peptide Lys Gly His[6] for wound healing, although no actual evidence of wound healing is provided. Koyama does not teach or suggest that this peptide reduces the damage done by ROS. Indeed, as acknowledged by the Examiner, Koyama does not teach or suggest anything about ROS.

The Examiner states that: "As it happens, at least some of the "damage" inflicted upon wounded tissue is caused by ROS." However, the Examiner has provided no evidence to support this statement, which he must do. See, *e.g.*, MPEP § 2142 (the examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness).

In particular, the Examiner has provided no evidence based on the prior art to support this statement, and it is submitted that the Examiner has improperly reconstructed the claimed invention through hindsight using Applicants' disclosure as a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner has not met in this case.

For the foregoing reasons, the Examiner has not even established a *prima facie* case of obviousness, and this rejection should be withdrawn.

13. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over Kimoto et al. *(Cancer Research*, **43**, 824 (1983)) in view of Ames (*Proc. Nat'l Acad. Sci.*, **90**, 7915 (1993)). It is the Examiner's position that:

> The teachings of . . . [Kimoto et al.] are indicated above. Ames discloses that various diseases are mediated by ROS, and further, that antioxidants can be used to mitigate the damage caused by ROS. Ames does not disclose the use of peptides which contain a histidine at third position from the N-terminus. . . . Thus, it would have been obvious that by administering an antioxidant peptide (as disclosed in . . . [Kimoto et al.]) to an animal afflicted with a ROS-mediated disorder, the damage caused by the ROS can be mitigated.

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[6] The peptide is Lys Gly His, not Gly Lys His, as stated by the Examiner.

Applicants respectfully traverse this rejection.

The peptides of the present invention are not bound to copper or any other metal when they are administered to animals. As result, the peptides bind metal ions present in the animals that cause the production or accumulation of ROS. See, *e.g.*, page 1, lines 7-13, and page 13, line 19 through page 14, line 2, of the present application. It is in this manner that the peptides of the invention reduce ROS and the damage that they cause.

Kimoto reports that a Cu(II)-Gly-Gly-His complex has anti-tumor activity when used in combination with a large amount of ascorbate (see the Abstract, the paragraph bridging columns 1 and 2 on page 827, and the final two paragraphs on page 827 of Kimoto). Contrary to the Examiner's contention, Kimoto does not teach or suggest that the peptide alone (*i.e.*, not complexed to copper) has such anti-tumor activity. Indeed, Kimoto teaches that it is the copper in the Cu(II)-Gly-Gly-His complex that is responsible for the killing of tumor cells (see the paragraph bridging columns 1 and 2, page 826, and third paragraph of Discussion, page 827, of Kimoto) and that the killing of the tumor cells is caused by ROS (see first full paragraph, column 1, page 827 of Kimoto and the entire Kimoto article).[7] Thus, Kimoto strongly teaches away from the present invention.

Ames adds nothing to the teachings of Kimoto. In fact, to the extent that Ames teaches "that various disease are mediated by ROS, and further, that antioxidants can be used to mitigate the damage caused by ROS," as contended by the Examiner, its teachings conflict with those of Kimoto.

Accordingly, the combined teachings of Kimoto and Ames would not have taught or suggested the presently claimed invention, and Applicants request that this rejection be withdrawn.

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[7] Kimoto further teaches that the Cu(II)-Gly-Gly His complex is ineffective in the absence of the ascorbate.

14. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over Konishi (U.S. Patent No. 4,461,724) in view of Ames (*Proc. Nat'l Acad. Sci.*, **90**, 7915 (1993)). It is the Examiner's position that:

> The teachings of . . . [Konishi] are indicated above. Ames discloses that various diseases are mediated by ROS, and further, that antioxidants can be used to mitigate the damage caused by ROS. Ames does not disclose the use of peptides which contain a histidine at third position from the N-terminus. . . . Thus, it would have been obvious that by administering an antioxidant peptide (as disclosed in . . . [Konishi]) to an animal afflicted with a ROS-mediated disorder, the damage caused by the ROS can be mitigated.

Applicants respectfully traverse this rejection.

Konishi was cited above by the Examiner as teaching the use of certain peptides having a histidine as the third amino acid from the N-terminus for the treatment of ulcers. However, as discussed above by Applicants, Konishi does not teach or suggest that these peptides reduce the damage done by ROS. Indeed, as acknowledged above by the Examiner, Konishi does not teach or suggest anything about ROS. Thus, contrary to the Examiner's contention, Konishi does not teach or suggest that the peptides taught by that patent are antioxidant peptides.

Ames does not teach or suggest that ROS are present in ulcers or that ROS cause any of the damage seen in patients suffering from ulcers. Also, as acknowledged by the Examiner, Ames does not teach or suggest peptides like those taught by Konishi or like those covered by the present claims for use as antioxidants.

It is apparent from the foregoing that even the combined teachings of Konishi and Ames would not have suggested to those skilled in the art that the peptides of the present claims could be used to reduce the damage caused by ROS. Indeed, it is submitted that there is no basis in the prior art for combining the teachings of Konishi and Ames and that the Examiner has failed to demonstrate the requisite motivation for combining the teachings of these two references.

It is also submitted that the Examiner has failed to establish even a *prima facie* case of obviousness. See, *e.g.*, MPEP § 2142. Instead, the Examiner has improperly reconstructed the

claimed invention through hindsight using Applicants' disclosure as a guide. Such impermissible hindsight reconstruction must be avoided in an obviousness evaluation. MPEP § 2142. The legal conclusion of obviousness must be reached on the basis of the facts gleaned from the prior art, MPEP § 2142, a standard which the Examiner has not met in this case.

For the foregoing reasons, the Examiner has not even established a *prima facie* case of obviousness, and this rejection should be withdrawn.

15. Rejection of Claims 1, 8-11, 21-26 and 28-31

The Examiner has rejected Claims 1, 8-11, 21-26 and 28-31 as being unpatentable over Pickart (U.S. Patent No. 5,118,665) in view of Ames (*Proc. Nat'l Acad. Sci.*, **90**, 7915 (1993)). . It is the Examiner's position that:

> The teachings of . . . [Pickart] are indicated above. Ames discloses that various diseases are mediated by ROS, and further, that antioxidants can be used to mitigate the damage caused by ROS. Ames does not disclose the use of peptides which contain a histidine at third position from the N-terminus. . . . Thus, it would have been obvious that by administering an antioxidant peptide (as disclosed in . . . [Pickart]) to an animal afflicted with a ROS-mediated disorder, the damage caused by the ROS can be mitigated.

Applicants respectfully traverse this rejection for the reasons given above in response to the rejection based on Pickart alone. Ames adds nothing to the teachings of Pickart. In particular, Ames does not contain any teachings which overcome, or any way diminish, the strong teaching away from the present invention by Pickart. Indeed, as acknowledged by the Examiner, Ames does not teach or suggest the use of peptides like those covered by the present claims. For all of the foregoing reasons, the Examiner is asked to withdraw this rejection.

E. Claims 21-26 and 28-31

In several of the Section 103 rejections, the Examiner states that Claims 21-26 and 28-31 "are rejected because the claims do not require that the peptide have any effect on the listed disorders, only that the animal be afflicted with one of the listed disorders." As noted in the present application, ROS play a major role in many diseases and conditions (see page 32, lines

15-16). Thus, since the peptides of the invention reduce ROS and the damage done by them, the peptides of the invention have a beneficial effect on numerous diseases and conditions, including those listed in Claims 21-26 and 28-31.

F. Information Disclosure Statements

Applicants are herewith submitting a supplemental information disclosure statement (IDS) listing those references stricken on the previous IDS's with the corrections desired by the Examiner with the exception of Reference 7 on the IDS received on 1/25/02. Applicants are still in the process of identifying the appropriate citation information for Reference 7. Applicants are also submitting herewith a copy of the reference not previously received by the Examiner.

CONCLUSION

It respectfully submitted that the pending claims are in condition for allowance, and a speedy allowance of them is requested.

Respectfully submitted,

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